balanced framework. Individual pain specialists and primary care doctors now need to work within this framework and collect data through good monitoring. Such data will be valuable when the recommendations are reviewed in March 2007.

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Reducing the transmission of genital herpes

Antiviral therapy is effective but should be used with safer sex practices and counselling

Seven years ago, an editorial published in this journal called for studies to clarify the role of antiviral treatment in preventing the transmission of genital herpes.[1] In the intervening years, seroprevalence studies in the United States have shown that the rate of infection with herpes simplex virus type 2 (HSV-2) has risen to 22%,[2] whereas in Europe, rates between 4% and 44% have been reported.[3] Support for an association between HSV-2 and HIV acquisition and transmission has increased, and anxiety about infecting their sexual partner is still among the top three concerns of people with genital herpes.[4–6] We know that antiviral treatment reduces symptomatic and asymptomatic shedding of HSV from genital mucosa,[7–9] but until now we have not known whether this would translate into a real, clinically important reduction in the transmission of genital herpes to an uninfected partner.

A recently published study was undertaken in 1484 heterosexual, immunocompetent couples to determine if daily valaciclovir could reduce the sexual transmission of genital herpes.[10] One partner of each couple had clinically diagnosed genital HSV-2 infection, and the other was HSV-2 seronegative. The infected partners were randomised to valaciclovir 500 mg once daily or placebo for eight months. Both partners were followed for clinical signs and symptoms of genital HSV infection, counselled on safer sex practices, and offered condoms at each visit. Symptomatic genital herpes was observed in the partners of 2.2% of individuals treated with placebo and 0.5% of those treated with valaciclovir (75% reduction in relative risk). Evidence (polymerase chain reaction, serology, or cell culture) of HSV-2 acquisition was present in 3.6% of couples in the placebo group and 1.9% of those in the valaciclovir group (hazard ratio 0.52, 95% confidence interval 0.27 to 0.99, P = 0.04). Genital herpes was less often transmitted in couples using condoms, but the benefit of valaciclovir was additional to the protective effect of condoms. None of the 141 individuals who took valaciclovir and used condoms for more than 90% of sexual encounters transmitted symptomatic genital herpes to their partner.

The rate of transmission in these monogamous HSV-2 discordant couples was very low, at under 5% over an eight month period, and we can speculate about reasons for this. Firstly, the study recruited women as the infected partners in 67% of couples, so most of the uninfected, seronegative partners were men. Men may be up to four times less susceptible to acquiring genital herpes than women (P = 0.006), so a low transmission rate was to be expected in this study.[11] Secondly, all couples enrolled in the study were motivated to try to prevent the transmission of infection and were explicitly advised to abstain from sexual intercourse during recurrences and to use condoms for every sexual encounter. Such measures are central to the current behavioural approach to reducing the risk of transmission of genital herpes. In assessing the cost effectiveness of this intervention in data from a population with such a low rate of sexual HSV transmission, it may therefore be valuable to model these effects in populations at greater risk of transmission. These include people who are less motivated to follow behavioural advice or in scenarios where people change sexual partners often. Also covariables should be examined, such as concurrent HIV transmission, to inform decision making on the public health effectiveness of this intervention in targeted groups.

In clinical practice, which individuals would benefit most from suppressive antiviral treatment to reduce the transmission of genital herpes to a partner? HSV-2 infection often goes undiagnosed and may be asymptomatic. Individuals with asymptomatic HSV-2 infection, even if diagnosed, will not themselves benefit from the suppressive effect of continuous antiviral therapy. However, if the risk of transmission of infection is causing anxiety even patients who do not find their own symptoms bothersome may benefit from a period of antiviral suppression, which can be linked to behavioural sexual health advice. Patients who are already taking suppressive drugs may find it reassuring to know that the medication they are taking to control their own symptoms is also helping to protect their sexual partner.

In the United States the results of this study have led the Food and Drug Administration to approve a new indication for valaciclovir—the prevention of sexual transmission of HSV infection. However, it must be emphasised that these new data were obtained in immunocompetent, heterosexual couples who were motivated to enrol in a trial. How the benefits will be altered by adherence to treatment or whether antiviral suppression affords protection of HSV transmission in other scenarios—such as during pregnancy, across same sex

BMJ 2005;330:157–8

relationships, or among individuals with HIV infection—requires measured clinical judgment until further studies are available. Furthermore, the vexed question remains of whether the notable reduction in transmission provided by valaciclovir would be achieved by other antiviral drugs, such as aciclovir or famciclovir, and if so, at what dose? Without comparative data, individual prescribing decisions in specific healthcare settings will need to be made on the basis of factors including availability, potential adherence, and cost.

That no evidence of viral resistance was detected in those individuals who became infected in this study is reassuring. That some susceptible individuals did become infected reinforces the message that valaciclovir reduced the frequency of HSV reactivation, subclinical shedding, and transmission of genital herpes, but it did not eliminate it. Antiviral treatment is thus not a substitute for other methods to control the spread of sexually transmitted infections but an additional tool. Patients should also be advised to continue using condoms, practise safer sex, and inform their partner about transmissible infections they have. The risk of transmitting genital herpes will not be removed, but patients can be assured that they are doing everything they can to reduce the risk of infecting a loved one.

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Schizophrenia: a genetic disorder of the synapse?

Glutamatergic synapses might be the site of primary abnormalities

Understanding the cause and pathogenesis of schizophrenia remains one of the great challenges in psychiatry. Progress has been slow, but one of the few certainties is that individual differences in liability are predominantly genetic.[1] This information has, however, not been useful neurobiologically because the genes themselves had not been identified. This situation is beginning to change, allowing a reappraisal of existing hypotheses of pathogenesis.

Until recently the two leading hypotheses concerned dopamine and neurodevelopment. The classic dopamine hypothesis, which attributed schizophrenia to a hyperdopaminergic state, arose from the ability of dopaminergic drugs to induce a psychosis, and the realisation that the potency of antipsychotic drugs is proportional to their ability to block dopamine receptors.[2] Refinements of the hypothesis indicate a more complex picture—increased dopaminergic transmission in the basal ganglia may underlie acute psychosis,[3] but a prefrontal cortical dopamine deficit is associated with neurocognitive impairments.[4] The dopaminergic changes are probably secondary to altered cortical glutamatergic transmission,[5] but compelling evidence for a primary causative abnormality in neurotransmission does not exist.

Whatever the fundamental causes of schizophrenia, clinical, epidemiological and neuroimaging studies clearly show that their influences are exerted from early in life and well before the changes in neurotransmission at the onset of acute psychosis.[6 7] Given robust findings that a number of brain regions are reduced in size, the absence of any pathological evidence for neurodegeneration is also consistent, albeit by default, with a neurodevelopmental model of schizophrenia.[8]

The positive findings from neuropathological studies are not conclusive, but now reasonable evidence exists for alterations in the cytoarchitecture of several brain areas, notably the hippocampus, the prefrontal cortex, and the dorsal thalamus where neurons, dendrites, synapses, and oligodendrocytes are affected.[8] Taken together, the findings imply an alteration in cortical circuitry, which may represent the anatomical basis of aberrant connectivity that has been inferred from neuropsychological and functional imaging studies.

These and other hypotheses of schizophrenia have been frustratingly vague, and although they provide clues to proximal causes of symptoms, they do not specify the causal molecular events. The situation, however, is now changing rapidly as several putative susceptibility genes have been discovered. Evidence for associations between DNA polymorphisms and schizophrenia has been reported and, more importantly, replicated for some of these genes.[9 10] The degree of agreement between studies sets these findings apart from numerous other claims made on the basis of single studies and makes it timely to consider how they affect the biology of the disease.

BMJ 2005;330:158–9